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10/616,880	07/10/2003	Benjamin David Silverman	YOR920030162US1	2640

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NEGIN, RUSSELL SCOTT	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/616,880	SILVERMAN, BENJAMIN DAVID	
	Examiner	Art Unit	
	RUSSELL S. NEGIN	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-9,14,15,17 and 19-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-9,14,15,17 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 18 November 2009 are acknowledged and the amendments are entered.

Claims 1, 3-5, 7-9, 14-15, 17, are 19-21 are pending, and examined in this Office action.

Withdrawn Rejection

The rejection of claim 21 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments filed to the instant claim on 18 November 2009.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following rejection is newly applied:

Claims 1, 3-5, 7-9, 14-15, 17, and 19-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 1, 14, and 21 each recite that "wherein each residue centroid having a same fractional distance to a surface of the tertiary protein structure as one or more additional residue centroids" wherein it is unclear as to the metes and bounds of a distance being measured in the same way (i.e. with the same dimensional units) as a centroid itself. For the purpose of examination, it will be interpreted that the same fractional distance is between the fractional distances of the questioned residue centroid from the center of the protein to the surface and the fractional distances of each of the one or more residue centroids from the center of the protein to the surface.

Independent claims 1, 14, and 21 continue to recite that that the equivalent magnitude associated with fractional distances is accomplished by a *mapping* procedure. It is unclear as to the metes and bounds of this mapping procedure (i.e. it is unclear as to the metes and bounds of residues being mapped to other locations within the protein).

Independent claims 1, 14, and 21 also recite that the first hydrophobic moment and the enhanced correlation between residue centroid magnitude and residue solvent accessibility are used to ***define*** a global linear hydrophobic moment. This limitation is indefinite because it is unclear as to the metes and bounds of a first hydrophobic moment and the enhanced correlation ***defining*** a global linear hydrophobic moment; the limitation is interpreted as (and would be clearer if it is amended to recite) a first hydrophobic moment and the enhanced correlation **calculating** a global linear hydrophobic moment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The following rejection is reiterated:

Claims 1, 3-5, 7-9, 14-15, 17, and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eisenberg et al. [Nature, volume 299, 1982, pages 371-274] in view of Silverman [PNAS; April 24, 2001; volume 98, pages 4996-5001] in view of Platt et al. [US Patent 5,784,294; issued 21 July 1998; filed 9 June 1995].

Claim 1 is drawn to a method for calculating a global hydrophobic moment of a tertiary protein structure comprising a plurality of residues. The method comprises calculating a centroid of residue centroids, using the centroid of residue centroids as a spatial origin of a global linear hydrophobic moment, calculating a first-order hydrophobic moment, and enhancing correlation between residue centroid magnitude and residue solvent accessibility, wherein the correlation between residue centroid magnitude and residue solvent accessibility is enhanced using a distance metric. The method also comprises using the first order hydrophobic moment and the enhanced correlation between residue centroid magnitude and residue solvent accessibility to define a global linear hydrophobic moment, wherein each of the residue centroids contributes a magnitude and direction to the global hydrophobic moment, and wherein

each residue centroid having a same fractional distance (measured for each residue centroid) to a surface of the tertiary protein structure contributes an equivalent magnitude (as additional centroid(s)) to the global linear hydrophobic moment by mapping each residue at a same distance from a center of the protein structure. The method further comprises using the global linear hydrophobic moment to characterize an amphiphilicity of a tertiary protein structure, and outputting the global linear hydrophobilc moment to a user. Each limitation of claim 1 is run on a system comprising one or more distinct devices using a tangible computer readable storage medium and a tertiary protein structure analyzer executing on a computer.

Claim 14 is drawn to the same subject matter as claim 1 wherein an apparatus is used for executing the method.

Claim 21 is drawn to the same subject matter as claim 1 wherein an article of manufacture is used for calculating a global hydrophobic moment of a tertiary protein structure.

Claims 3-4 and claims 19-20 are further limiting with the additional limitations that the correlation between the residue centroid magnitude and the residue solvent accessibility is enhanced by using an ellipsoidal metric and a solvent accessibility metric, respectively.

Claim 5 and claim 15 are further limiting with the additional limitation that the centroid of residue centroids represents a geometric center of the tertiary protein structure.

Claims 7-9 and claim 17 are further limiting with the additional limitations that the global linear hydrophobic moment characterizes the magnitude of amphiphilicity, direction of amphiphilicity, and identification of functional regions in the tertiary protein structure, respectively.

The article of Eisenberg et al. studies use of a first order helical hydrophobic moment to measure the amphiphilicity of a helix.

The abstract on page 371 of Eisenberg et al. quantifies the mean hydrophobic moment as a vector sum of all of the first order hydrophobic moments of the residues constituting the helix.

Figure 1 of page 372 of Eisenberg et al. illustrates a vector sum for a helix to determine a global (i.e. mean) hydrophobic moment for a protein helix. Each residue in the helix contributes a magnitude and direction of the global hydrophobic moment.

Figure 2 on page 374 of Eisenberg et al. plots the hydrophobic moments of helices of different proteins as a function of the degree of hydrophobicity/amphiphilicity of each of the helices in the study. It is also noted that the plot in Figure 2 of Eisenberg et al. displays the magnitude of the first-order hydrophobic moment as a function of the hydrophobicity which is defined as the equivalent of a zero order (linear) hydrophobic moment in Eisenberg et al. (i.e. see second full paragraph in column 2 of Eisenberg et al. on page 372).

Figure 2 of Eisenberg et al. also demonstrates an enhanced correlation between residue magnitude and residue solvent accessibility, wherein the correlation between residue moment magnitude and residue solvent accessibility is enhanced using a

distance metric. Specifically, the ordinate axis of Figure 2 of Eisenberg et al. demonstrates a residue moment magnitude which is then correlated to solvent accessibility (i.e. "Globular," "Surface," and "Membrane,") within the plot of Figure 2 of Eisenberg et al.

However, Eisenberg et al. does not use residue centroids as the origins in the hydrophobic moment calculations (instead, alpha carbons are used as reference points), and Eisenberg et al. does not show the computer hardware and software limitations of the instant claims. Furthermore, while Figure 1 is also an output of the global linear hydrophobic moment for an alpha helix wherein each residue in Figure 1 has a different distance, the distances in Figure 1 of Eisenberg et al. do not constitute a fractional distance as a ratio of the moment magnitude to the distance from the center point to the surface of the protein. Additionally, Eisenberg et al. does not teach the computerized limitations of the instant set of claims.

The article of Silverman, "Hydrophobic moments of protein structures: Spatially profiling the distribution," describes how to calculate moments of tertiary protein structures.

In equation [12] on page 4997 of Silverman, r_i is the vector pointing to the centroid of residue *i* while r_c is the vector pointing to the centroid of the entire protein molecule (i.e. the geometric center of the protein).

In equation [13] on page 4998 of Silverman, a first order hydrophobic moment imbalance about the entire protein is derived, accounting for hydrophobicity and solvent

accessible surface area. Each centroid of every protein residue contributes to this global moment.

In equations [13] and [14] on page 4998 of Silverman, distance metrics, ellipsoidal metrics, and a solvent accessibility are all used to enhance the centroid magnitude.

Pages 4998-5000 of Silverman illustrate the computation of global linear (i.e. zero order) hydrophobic moments for entire proteins.

Additionally, page 4998, column 2 teaches the obtaining of protein structures from the Internet, and page 5000, column 2, paragraph 2 teaches obtaining protein structures from the PNAS website.

Figure 6 on page 5000 of Silverman shows how an arm of the protein can be identified as it falls outside the ellipse characterizing the hydrophobic moment of the protein.

Additionally, Figure 3 of Silverman is interpreted to teach fractional distances between the center point of the plot and surface of the protein (i.e. the outermost ellipse). Specifically, Figure 3 is a cross-section of the alpha-helix of 1AKZ, with the outermost ellipse being interpreted as the surface of the protein as it is includes every amino acid [see paragraph bridging columns 1 and 2 of page 4999 of Silverman]. As there is no single pair of centroids with the SAME fractional distance to the surface of the protein there are no pairs of centroids that contribute an equivalent magnitude to the global linear hydrophobic moment by mapping each residue at a same distance from the center of the protein structure.

However, Eisenberg et al. and Silverman do not teach the computerized limitations of the instant set of claims.

Platt et al. teaches a system and method for comparative molecular moment analysis. Specifically, Figure 1 of Platt et al. illustrates computerized limitations that are interpreted to be computer system and a structure analyzer for the purpose of identifying molecular moments as described in the abstract.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the helical hydrophobic moment study of Eisenberg et al. by use of the hydrophobic moment study of Silverman wherein the motivation would have been that using residue centroids instead of atomic points yields a more ideal overall shape and moment of the protein (see first full paragraph of column 1 on page 4998 of Silverman). There would have been a reasonable expectation of success in applying the moment analysis of a single helical secondary structure (i.e. Eisenberg et al.) to the entire protein structure (i.e. Silverman) because the mathematical vector analysis is general and not locally restricted to single secondary structural elements.

It would have been further obvious to use fractional distances in Silverman to substitute for absolute distances in Eisenberg et al. because it is obvious to substitute one known element in the prior art for a different element. In this instance the fractional distances of Silverman are an alternate means of analyzing the geometry of a protein. There would have been a reasonable expectation of success in combining the studies of Eisenberg et al. and Silverman because they both pertain analogously to protein hydrophobic moment calculations.

It would have been further obvious to modify the hydrophobic moment analyses of Eisenberg et al. and Silverman by use of the computerized moment analysis of Platt et al. wherein the motivation would have been the provides a faster and more efficient means of executing the claimed invention [see Figure 1 and column 4, line 55 to column 5, line 10 of Platt et al. for examples of the powerful computing techniques in Platt et al.].

Response to arguments:

Applicant's arguments filed 18 November 2009 have been fully considered but they are not persuasive.

Applicant begins by arguing on page 10 of the Remarks that Figure 2 of Eisenberg et al. that hydrophobicity and solvent accessibility are two separate entities; since the abscissa of Figure 2 plots hydrophobicity and not solvent accessibility, and even if these entities are related, Eisenberg et al. does not demonstrate an enhanced correlation between centroid magnitude and solvent accessibility. This argument is not persuasive because Figure 2 of Eisenberg et al. also imprints on the plot three different types of solvent accessibilities ("Globular," "Surface," and "Membrane") along the abscissa of the plot. Consequently, the hydrophobic moment is plotted against solvent accessibility such that there is an enhanced correlation between the two entities.

Applicant additionally argues that the argument in the previous paragraph allegedly contradicts statements in previously submitted Office action. This argument is

not persuasive because the instant Office action is the most current assessment and analysis of the instant set of claims.

Applicant additionally argues that the instant reference does not teach that when a pair of centroids has the same fractional distance to the surface of the protein, each member of the pair must contribute the same magnitude to the linear moment. However, this argument is not persuasive because the limitation is met in Eisenberg et al. and Silverman. The instantly amended claim does not require that if each member of the pair of residue centroids were to **HAVE** a same fractional distance to a surface of the tertiary protein, each member of the pair would contribute an equivalent magnitude to the global linear hydrophobic moment by mapping. Instead, the instantly amended claim recites "wherein each residue **HAVING** a same fractional distance to a surface of the tertiary protein structure… contributes an equivalent magnitude to the global linear hydrophobic moment by mapping…" As no one of the residue centroids of Silverman (i.e. Figure 3) has the same exact fractional distance as a second residue centroid, this limitation is met in Eisenberg et al. and Silverman (i.e. because no two residues have the exact same fractional distance, there is no mapping to be carried out).

Applicant additionally argues with regard to the document of Platt et al. that Platt et al. uses automation for a distinct process that the automation in the instant application. This argument is not persuasive because Platt et al. demonstrates automation for an analogous study of protein properties (i.e. the same field of invention as the instant application). Platt et al. is a supporting reference used solely to teach that it is obvious to automate the calculations of the instant invention.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 8:30 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only.

For more information on the PAIR system, contact the Electronic Business Center

(EBC) at 866-217-9197 (toll-free).

/Russell S. Negin/
Examiner, AU 1631
21 January 2010